TOXICOLOGIST'S REVIEW

BLA: STN 125058
SPONSOR: Biomarin Pharmaceutical Inc.
PRODUCT: recombinant human a-iduronidase; rhIDU; laronidase; Aldurazyme™
FORMULATION/CHEMISTRY: Isolated from cell culture supernatant after growth of CHO cells transfected with a recombinant expression vector encoded for rhIDU. Formulated as a sterile, liquid solution of polysorbate 80 (10 µg/ml, 0.05 mg) in a sodium chloride (150 mM, 43.9 mg) and sodium phosphate buffer (92 mM, 63.5 mg). The drug product is to be diluted for intravenous administration with between 100ml to 250ml of 0.9% sodium chloride solution. The final product (2.90 mg/ vial, 100 units/ml), is reconstituted with 5 mL of Water for Injection USP.
PROPOSED INDICATION: Long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; a-l-iduronidase deficiency) to treat the non-central nervous system manifestations of the disease
ABBREVIATIONS: recombinant human a-iduronidase = rhIDU, intravenous = IV, glycosaminoglycan = GAG; MPS I = Mucopolysaccharidosis I, (α-L-iduronidase deficiency)

Application History

BL125058/0.00: Original submission of rolling BLA 26-JUL-2002
BL125058/0.01: Preclinical Toxicology Update 04-SEP-2002
BL125058/0.02: Neutralizing Antibody Data for Phase 3 (ALID-003-99) 10-OCT -2002
BL125058/0.03: Additional Dataset % Predicted Normal FVC Phase 3 (ALID-003-99) 17-OCT -2002
BL125058/0.04: 36-Week Efficacy Data for Phase 3 Ext. (ALID-006-01) 24-OCT-2002
BL125058/0.05: 120-Day Update 05-DEC-2002
BL125058/0.06: Responses to the Discipline Review Letter for the CMC 09-DEC -2002
BL125058/0.07: 120-Day Update: CRTs & Programs 12-DEC-2002
BL125058/0.08: Clarification: Number of Bioreactors for Cell Culture of Laronidase 19-DEC –2002

CROSS-REFERENCES: BB-IND ----------

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Introduction

The target agent, Aldurazyme™ (laronidase) is a recombinant form of human a-iduronidase enzyme, which is a monomeric protein with a molecular weight of 83kD by ---------- analysis. Laronidase is a 628 amino acid lysosomal hydrolase that cleaves iduronic acid residues from the non-reducing ends of heparan sulfate and dermatan sulfate. The enzyme is a single polypeptide chain of molecular mass ---------- ---------- and a molecular formula of ---------- contains six asparagine-linked glycosylation sites, two of which carry the bis mannose-6-phosphate oligomannose$_7$ oligosaccharide that binds the target cell surface receptor. The apparent increase in molecular mass of -- kD over that predicted by the amino acid sequence is a result of posttranslational modifications.

Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder located at 4p16.3. In the human, α-L-iduronidase deficiency results in a spectrum of clinical manifestations and disease severities. These manifestations are directly related to accumulation of glycosaminoglycans (GAGs), primarily dermatan and heparan sulfate, as a result of the lysosomal enzyme deficiency. The clinical spectrum is conventionally categorized into three overlapping clinical syndromes that vary in clinical severity. These are in order of decreasing clinical severity, Hurler syndrome (MPS1H), Hurler-Scheie Syndrome (MPS IH-S), and Scheie Syndrome (MPS-IS). The three syndromes are indistinguishable on the basis of the routine clinical chemistry measures as all three exhibit only minimal enzyme activity and all show elevated urinary GAG levels the ranges of which overlap. Further although the classical diagnostic criteria are clinical,

they also overlap and the designation of an individual into a particular diagnostic category is somewhat subjective. In general Hurler patients present within the first year multiple of the following findings: coarse facies, skeletal deformities, prominent forehead, hernia (umbilical or inguinal), enlarged tongue, short stature, joint stiffness, acute cardiomyopathy associated with endocardial fibroelastosis, developmental delay that progressively increases, deafness, recurring upper respiratory tract and ear infections, obstructive airway disease, sleep apnea, noisy breathing, persistent copious nasal discharge, corneal clouding, and occasionally communicating hydrocephalus associated with increased intracranial pressure. Death usually occurs within the first decade of life. Patients classified as Hurler-Sheie patients typically present later (between the ages of 3 and 8) with milder symptoms. These symptoms include hepatosplenomegaly, obstructive airway disease and sleep apnea, recurring respiratory infections, dysostosis multiplex, short stature, characteristic coarse facies, corneal clouding, joint stiffness, deafness, and valvular heart disease. The life expectancy for these patients is to reach young adulthood. Unlike Hurler patients, Hurler-Scheie patients achieve normal developmental milestones. The patients with the mildest MPS I deficiency phenotype, Sheie Syndrome are usually diagnosed in the teen years and the presenting symptoms are often joint stiffness, aortic valve disease, mild hepatosplenomegaly or corneal clouding. These patients have little or no neurological manifestations, a normal stature and may live a normal lifespan with only minimal clinical symptoms and few restrictions on activities of daily living.

The proposed clinical indication for Aldurazyme™ (laronidase) is “long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; α-L–iduronidase deficiency) to treat the non-central nervous system manifestations of the disease”. In the submitted package insert the sponsor recommended the following dosage regimen-

“The recommended dosage regimen of Aldurazyme™ is 100 U/kg (0.58 mg/kg) of actual body weight administered once weekly as an intravenous infusion.”

With initial administrations of Aldurazyme™, it is recommended that patients be administered pretreatment medications approximately 60 minutes prior to the start of the infusion. If clinically indicated, the administration of pretreatment medications should continue with subsequent infusions of Aldurazyme™.

The total volume of the infusion is determined by the patient's actual body weight and should be delivered over approximately 3 to 4 hours. Patients with an actual body weight of 20 kg or less should receive a total volume of 100 mL. Patients with an actual body weight of greater than 20 kg should receive a total volume of 250 mL. The initial infusion rate of 2 U/kg/hr may be incrementally increased every 15 minutes during the first hour, as tolerated, until a maximum infusion rate of 43 U/kg/hr is reached. The maximum rate is then maintained for the remainder of the infusion (2-3 hours).

Each vial of Aldurazyme™ contains 500 U (100 U/mL; 0.58 mg/mL) of laronidase and is intended for single use only. The concentrate for solution for infusion must be diluted with 0.1% Human Serum Albumin in 0.9% Sodium Chloride for Injection, USP using aseptic techniques. In the absence of stability studies using glass containers, it is recommended that Aldurazyme™ be prepared and administered using PVC Containers. It is recommended that the Aldurazyme™ solution be administered with a PVC infusion set equipped with an in-line, low protein binding 0.2 micrometer (µm) filter.

The primary trial used to demonstrate Aldurazyme™ was a single randomized, placebo-controlled clinical trial of 45 MPS I patients, of whom 1 was classified as having the Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients had a baseline forced vital capacity (FVC) less than or equal to 80% of predicted. Patients received Aldurazyme™ at 0.58mg/kg or placebo once weekly for 26 weeks. In clinical studies the most significant adverse reactions were infusion related-reactions of varying clinical intensities as were seen in the preclinical studies. As a result in the Phase 3 Studies, all patients were pretreated prior to each infusion with age-appropriate dosages of antihistamines and antipyretics, such as diphenhydramine or hydroxyzine and acetaminophen or ibuprofen, respectively.

The principal efficacy outcome assessments were FVC and distance walked in 6 minutes (6 minute walk test, 6MWT). After 26 weeks, AldurazymeTM-treated patients showed improvement in FVC and in the 6MWT compared to placebo-treated patients. Evaluations of bioactivity were changes in liver size and urinary GAG levels. Liver size and urinary GAG levels were decreased in Aldurazyme™ treated patients compared to placebo-treated patients. No subject in the Aldurazyme™-treated group reached the normal range for urinary GAG levels during this study.

Preclinical Pharmacology Studies

Notes of clarification

Note that during preclinical development of rhIDU drug product, the assay for a-L-iduronidase activity was changed to make it more reproducible and robust and the definition of a unit was changed to be more conventional. In addition, the ---
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----------The sponsor provided an overview of the doses administered in all studies with dose conversions for all studies in the BLA submission. For clarity, doses are presented in mg/kg utilizing the new units throughout this BLA review, in order to facilitate comparison to the recommended human dose.

Also note that the dates presented with each study are the dates the report was issued, not the date of study completion when report issued date is available. This convention will be used throughout this BLA review.

Assay for rhIDU activity in animal studies

List of Pharmacology Studies

1. IDU-PC-002: Short-term Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in a Single Dog, non-GLP, Conducted at----------, 11/93, Lots no. ----------

2. IDU-PC-003: Acute intravenous infusion study of recombinant human α-L-Iduronidase in a single dog; non-GLP, Conducted at----------, 4/95, Lots no. -----

3. IDU-PC-004: Subchronic Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in Dogs: 4/94, non-GLP, Conducted at----------, Lots nos. -----

4. IDU-PC-005: Thirteen-Month Intravenous Infusion Study of Recombinant Human a-L-Iduronidase in a Dog: non-GLP, Conducted at----------, 1/95, Lot nos. -----

5. IDU-PC-006: 74-Week Intravenous Infusion Study of Recombinant Human a-L-Iduronidase in Dogs: 3/99, non-GLP, Conducted at----------, Lot nos. ----------

6. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human α-L-Iduronidase in Dogs, non-GLP, Conducted at ----------, 02/01, Lot no. ---.

7. Kakkis et al.: Enzyme replacement therapy in feline mucopolysaccharidosis I, N/A, Lot nos. -----

Review of Pharmacology Studies

1. IDU-PC-002: Short-term Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in a Single Dog: Multi-step intravenous dose regimen study in a single dog. Part 1- 0.116mg/kg IV every other day for 7 doses (12 days), part 2 - IV three doses every other day for 5 days starting two months after the first dose, part 3- one IV dose (0.116 mg/kg) five months after the first dose. Levels of IDU increased in liver biopsy after treatment. Histopathology reportedly shows decreased cellular vacuolation in live and normalization of the histology of hepatocytes and Kupffer cells.

2. IDU-PC-003 One control female MPS I dog and two laronidase treated 0.58 mg/kg IV (one male and one female) MPSI dogs every other day for 5 doses (days1, 2,5,8,10) with sacrifice on day 12. Levels of IDU increased relative to untreated MPS I dogs in all tissues sampled (liver, spleen, lung, kidney, cerebrum, heart valve, myocardium, lymph node, and cornea).

3. IDU-PC-004: Subchronic Intravenous Infusion Study of Recombinant Human α-L- Iduronidase in Dogs. 2 untreated MPS I dogs and 3 MPS I dogs treated intravenously with 0.116 mg/kg rhIDU weekly for 3 months. Levels of IDU in liver greater than that in normal dog liver and spleen, other tissues less than normal dog but elevated relative to MPS I control. Histopathologic analysis showed decreased cellular vacuolation in liver, kidney and spleen.

4. IDU-PC-005: Thirteen-Month Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in a Dog. Study of weekly intravenous infusion of 0.116 mg/kg for 74 weeks. Activity of a-L-Iduronidase increased in all tissues measured versus control levels in MPS I dog. Levels of IDU in liver greater than that in normal dog liver, other tissues less than normal dog but elevated relative to MPS I control. The GAG accumulation was decreased but still above normal. Histopathologic analysis showed persistent GAG accumulation in liver, kidney, adrenal gland, lung, lymph node, small intestine, spleen, synovium, gall bladder despite decreased cellular vacuolation.

5. IDU-PC-006: 74-Week Intravenous Infusion Study of Recombinant Human α-L-Iduronidase in Dogs: Uncontrolled intravenous dose-ranging study in MPSI dog model. Two dogs dosed with 0.058-0.58 mg/kg IV 1-2 times a week for weeks 1-7, then with 0.58 mg/kg IV 3 times a week for weeks 8-46, then once per week with 0.58 mg/kg IV for weeks 47-74. Results show a-L-Iduronidase activity approaching normal in liver, intestine, kidney, lung, lymph nodes, spleen, myocardium, synovium, and rib cartilage, all other tissues are less than normal. GAG accumulation decreased in all tissues relative to beginning and still above normal. Histopathology show depleted accumulation in macrophages in all tissues except CNS and dense connective tissue. Clinical improvement noted.

6. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human α-L-Iduronidase in Dogs: Two untreated and seven treated MPS I dogs were treated intravenously with laronidase. Two animals treated with 0.58 mg/kg and three with 2.32 mg/kg for continuous infusion for 10-39 weeks, and two dogs treated weekly for 10 weeks. Results show a-l-Iduronidase activity increased in all tissues measured relative to MPSI control animals. Levels were greater than normal canine levels in liver, spleen, kidney, lymph nodes, rib cartilage, synovium, and tracheal cartilage after both continuous and bolus infusions. GAG accumulation decreased to within or > 2-fold the normal range for kidney, liver, lung, lymph nodes, spleen, and synovium after more than one dosing interval. No reductions seen in heart valve or brain. Histopathologic information in macrophages, lymph nodes, spleen and liver reduced more by bolus than continuous infusion and with a positive dose response. No decrease in GAG vacuolation in CNS or dense connective tissue.

7. Kakkis et al., Mol. Genet. Metab. 2001. Dose ranging study in MPS I deficient cats. MPS I cats were treated intravenously for up to six months. Three were treated with 0.116 mg/kg weekly for three months, one was treated with 0.58 mg/kg IV weekly for three months in the first part of the study. In the second part of the study, one cat was treated with 0.116 mg/kg IV weekly and one cat was treated with 0.58 mg/kg IV weekly for six months. The a-L-Iduronidase activity was increased relative to controls with all tissues measured except brain, and rib cartilage, GAG accumulation was decreased to the normal range in liver, spleen and lung.

PK/ADME Studies

List of PK/ADME Studies

1. IDU-PC-001: Clearance and Tissue Distribution Study of Recombinant Human α-L-Iduronidase in Dogs: non- GLP, Conducted by ----------9/93, Lots no. ----------

2. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human a-L-Iduronidase in Dogs, non-GLP, Conducted at ----------, 2/01, Lot no. ----.

Review of PK/ADME Studies

1. IDU-PC-001: Clearance and Tissue Distribution Study of Recombinant Human α-L-Iduronidase in Dogs: One female MPS I dog was treated daily with 0.116 mg/kg for days 1 and 2. Result: Biphasic clearance: $t_{1/2}$ α = 0.9 minutes, $t_{1/2}$ β = 18.9 minutes.

2. IDU-PC-008: Comparison of Continuous and Bolus Intravenous Infusions of Recombinant Human a-L-Iduronidase in Dogs: Two MPS I dogs (one male, one female) were treated once during weeks 2 and 10 with 2.32 mg/kg IV. Results: Week 2- Biphasic clearance, $t_{1/2}$ α = 0.9 minutes, $t_{1/2}$ β = 59.5 and 94.9 minutes. Week 10- Monophasic clearance, $t_{1/2}$ = 66.2 and 23.8 minutes. V_c = approximately 60 ml/kg. AUC (U/ml-hr) increased from week 2 (269 and 407) to week (13364 and 2559). Clearance from (ml/kg/min) decreased from week 2 (31.0 and 20.5) to week 10 (0.62 and 3.26).

Preclinical Toxicology Studies

List of Preclinical Toxicology Studies:

1. IDU-PC-007: An acute intravenous toxicity study in rats. GLP, conducted at---------- No. 0406RB31.001, 3/01, Lot No.----------.

2. IDU-PC-009: 26-week intravenous infusion toxicity study with recombinant human a-L-Iduronidase in monkeys with a 2-week recovery: ----------monkeys----------, GLP, Conducted at ----------. 6354-122), 8/02, Lot No. PD-01-01 (from Lot ----------)

3. IDU-PC-011: Effect of repeat intravenous administration of recombinant human α-L-Iduronidase with and without canine serum albumin to ------ dogs (---------- No. 6354-130), GLP, Conducted at ----------, 1/02, Lot No. PD-01-01 (from Lot ----------.

4. IDU-PC-012: A one-day evaluation of the hemodynamic effects of the administration of Aldurazyme™ (laronidase for injection) to dogs during a 4-hour infusion. GLP, conducted by ----------No. R-032), 9/00, Lot nos. ----------

5. IDU-PC-013: Intravenous fertility and general reproduction toxicity study of alpha-L-Iduronidase in rats: GLP, Conducted by ---------- Protocol Number 907-008, Biomarin Study Number 01035, 8/02, Lots no. ----------

6. IDU-PC-014: Intravenous developmental toxicity study of alpha-L-Iduronidase in rats; GLP, Conducted by ----------No. 907-007; Biomarin Study Number: 01037, 8/02, Lots no. ----------

Review of Preclinical Toxicology Studies:

Acute Toxicity Studies

1. **IDU-PC-007: An acute intravenous toxicity study in rats:**
   Species: ----------rats
   Dose Levels: 0, 0.29, 0.58, 5.8 mg/kg
   Route Duration: single IV bolus, + kills on day 15.
   Methods: Clinical signs, BW, clinical pathology, gross & histopathology**.**
   Findings: No abnormalities in BWs, clinical pathology, organ weights. Incidental gross finding of single pale focus in liver in a male (5.8mg/kg group). Increase in number (but not incidence of sporadic findings of small foci of hepatocellular necrosis).

   The NOAEL was ≤ 0.58 mg/kg

2. **IDU-PC-012: A one-day evaluation of the hemodynamic effects of the administration of Aldurazyme™ (laronidase for injection) to dogs during a 4-hour infusion: General GLP adherence**
   Species: ---------- dogs (2 females)
   Dose Levels: 0.7 mg/kg, 3.9 mg/kg, 4.9 mg/kg
   Route Duration: IV x 2 approximately 4 hour infusion. Low and high doses in each animal after a 30 minute space (one high dose 3.9 mg/kg & one high dose 4.9 mg/kg).
   Methods: Cardiovascular (EKG, BP) monitoring, kill same day as treatment 30 minutes after high dose treatment.
   Findings: No treatment related abnormalities in EKG or HR.

   The NOAEL was ≤ 4.9 mg/kg

Multidose Toxicity Studies

1. **IDU-PC-009: 26-week intravenous infusion toxicity study with recombinant human a-L-Iduronidase in monkeys with a 2-week recovery: ---------- monkeys----------:**

Species: ---------- monkeys ----------

Dose Levels: 0, 0.166, 1.659, 16.588 (5/sex/group)

Route Duration: IV bolus (7 hour infusion) weekly for 26 weeks.

Methods: Clinical signs, BW, clinical pathology, gross & histopathology, ophthalmic examinations, antibody analysis, toxicokinetics.

Findings: Monkey (152259) developed hypersensitivity with edema around eyes and muzzle half way through the fourth dose. No treatment-related abnormalities in food consumptions, organ weights, sperm counts or morphology, gross, or histopathology. Decrease in BW of females in low and mid-dose (0.166, 1.659 mg/kg) at week 26, no effect in high dose group.

Clinical pathology- All monkeys in the high dose groups (male & female) 16.588 mg/kg have increased total leukocyte, lymphocytes and eosinophil counts, and monocyte counts (female) at one or more treatment groups. The changes (except eosinophil in male, and monocyte in female) resolved during the recovery period. No specific clinical sequelae of these changes were seen.

Antibody assays-

Approximately half the animals had increased levels of antibodies at 26 weeks versus the levels at 13 weeks. The animals that developed antibodies to rhIDU developed them to various levels (61.2-8843.9 A_{450} units per µL serum at week 26). The response does not appear to be dose related. There was no difference in antibody levels due to sex.

Pharmacokinetics- Serum rhIDU levels were insufficient at 0.166 mg/kg to perform pK analysis. Decreased AUC in 1.659 mg/kg group at 1, 13 and 26 weeks, but not seen at high dose (16.588 mg/kg). Liver levels of rhIDU determined and found to be dose-related.

The NOAEL was 1.659 mg/kg

2. **IDU-PC-011: Effect of repeat intravenous administration of recombinant human** a **-L-Iduronidase with and without canine serum albumin to ------ dogs:**

Species: ------ dog

Dose Levels: 0, 1.6 mg/kg

Route Duration: IV 4 hour infusion once a week for 8 weeks.

Methods: Clinical signs, BW.

Findings: All formulations induced facial edema, emesis, mucoid stools and/or

excessive salivation starting at the third dose. The severity of clinical effects were ranked thus: rhIDU> rhIDU with dog serum> rhIDU with Tween 80.

Reproductive/Developmental Toxicity Studies

1. IDU-PC-013: Intravenous fertility and general reproduction toxicity study of alpha-L-Iduronidase in rats:

Species: ----------rats (25/sex/group)

Dose Levels: 0, 0.036, 0.36, 3.6 mg/kg/day for rhIDU and 5mg/kg for diphenhydramine (DPH) pretreatment for all rhIDU doses including a vehicle control.

Route Duration: IV bolus for rhIDU and DPH. Male rats – rhIDU daily for 21 days prior to cohabitation for a total of 28 days (DPH days 9-35). Female rats – Daily rhIDU 15 days before cohabitation and until DG7 (DPH day 1 of study until DG7). Male sac at day after mating, female at DG 21.

Methods: Clinical signs, BW, food consumption, vaginal smears, sperm evaluation, gross & histopathology.

Findings: Female: Reduction of increase in weight in DPH, 0.036, 3.6 mg/kg groups for DS 8 to 15. No Rx-related biological effects on clin signs, food consumption, gross path, estrous cycles – normal. Male: Testes/prostate/seminal vesicles/epididymides wts - comparable between groups. No adverse effects on sperm motility, sperm counts, sperm morphology

Mating indices= 100%/100%/100%/100%/100% at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Pregnancy rates = 96%/87.5%/92%/91.7%/88% at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Mean percent preimplantation loss per rat [corpora lutea minus implants] = 12/10/12/17/10 at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Mean percent postimplantation loss per rat [implants minus live fetuses] = 2.5/3.6/3.9/3.2/4.2 at 0/DPH (5)/0.036/0.36/3.60 mg/kg

Mean number of live fetuses per rat = 15.4/14.7/15/14/14.8 at 0/DPH(5)/0.036/0.36/3.60 mg/kg

2.**IDU-PC-014: Intravenous developmental toxicity study of alpha-L-Iduronidase in rats:**

Species: ---------- rats (25 female rats/group)

Dose Levels: 0, DPH (5), 0.036, 0.36, 3.6 mg/kg

Route Duration: Slow IV bolus daily on DGs 7 through 17.

Methods: Clinical signs, BWs, food consumption, vaginal smears, TK profile, pregnancy rate, uterine contents, ovary evaluation, gross evaluation, fetal exams

Findings: There were statistically significant reductions in body weight gains (DGs10-12) in the 0.36 and3.6 mg/kg/day groups and in the food consumption on days 15 to 18 in the 0.36 and 3.6 mg/kg groups. No adverse effects on clinical signs, estrous cycles, gross pathology

Mating indices= 100% - all groups

Pregnancy rates = 88%/96%/84%/96%/100% at 0/DPH (5)/0.036/0.36/3.6 mg/kg

Mean percent preimplantation loss per rat = 6.4%/6.3%/11%/8.3%/3.2% at 0/ DPH (5)/0.036/0.36/3.6 mg/kg

Mean percent postimplantation loss per rat = 3.2%/3.8%/2.9%/1.7%/2.4% at 0/ DPH (5)/0.036/0.36/3.6 mg/kg

Mean number of live fetuses per rat = 14.3/14/13.1/14.5/14.4 at 0/ DPH (5)/0.036/0.36/3.6 mg/kg

F1 Fetuses - No Rx-related effects on BWs, external, visceral, or skeletal anomalies

The NOEL was 0.036 mg/kg/day for parental toxicity and for fertility & reproductive performance. The NOEL for embryotoxicity was >3.6 mg/kg/day.

Mutagenicity Studies

No studies were performed.

Carcinogenicity Studies

No studies were performed.

Safety Pharmacology Studies

No studies were performed.

Conclusion

Aldurazyme™ is a highly purified and well-characterized 83 kD glycoprotein. It is isolated from cell culture supernatant after growth of CHO cells transfected with a recombinant expression vector encoded for rhIDU The proposed clinical indication is the long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I; a-l-iduronidase deficiency) to treat the non-central nervous system manifestations of the disease. The safety, efficacy, pharmacokinetics and biodistribution of recombinant human a-L-iduronidase (rhIDU) have been evaluated using studies in four species (dog [MPS I and wild-type], MPS I cat, ---------- monkey, and ---- rat) of animals. The results of those studies demonstrate that rhIDU has an acceptable safety profile, with no consistent, treatment-related toxicity other than the immune reaction of the animals to a foreign protein and/or other constituent of the product. The most significant treatment-related finding seen in the preclinical studies was an anaphylactoid reaction that occurred in several dogs in early pharmacology studies. Reoccurrence of this event was prevented in most of the later studies by pharmacological pretreatment of the animals and changes in the dosing solution and regimen, however a significant infusion reaction occurred in the---------- monkey study during administration of the fourth dose. The animal had not been pretreated.

Two species (dog and cat) provide natural animal models of the MPS I disease, and a ---------- mouse model has been described (but not submitted in the BLA application)(Haskins 1997, He 1999, Clarke 1997). The naturally occurring feline MPS I model the disease is a result of a----------. The canine model is maintained in a mixed breed colony manifestations seen in naturally occurring disease is remarkably

similar in three species known to have natural disease, human, cat, and dog. The manifestations emanate from a marked deficiency of the lysosomal enzyme, α-L-iduronidase which is manifested universally by excessive urinary dermatan sulfate and heparan sulfate. The clinical features in all three species include facial dysmorphia, corneal clouding, cardiac valvular insufficiencies and bone disease. Felines affected by the disease do not manifest the growth delay that is a prominent feature in human and canine disease, but do survive to reproductive age, as do canines and humans. The sponsor has submitted seven studies in naturally occurring models of disease (six MPS I canine studies, one MPS I feline study) as pharmacodynamic studies to support the rationale of biological effectiveness in of the product, Aldurazyme™.

The MPS I canine studies submitted (IDU-PC-002, IDU-PC-003, IDU-PC-004, IDU-PC-005, IDU-PC-006, IDU-PC-008) are intravenous studies that explore dose and dosing regimens. The studies used a total of 28 dogs including controls. The consistent pharmacologic finding in these studies was that the treatment decreased GAG accumulations in the liver. This finding was seen across the 20U/kg/week to 100U/kg/week dose range and across various dosing regimens (single IV dosing, every other day dosing, and continuous infusions). Although longer duration studies (IDU-PC-005, IDU-PC-006) also reduce GAG accumulations in additional tissues such as kidney, spleen, adrenal gland, lymph nodes, small intestine, joint synovium, and gall bladder as measured by histology, histological evaluation failed to demonstrate a reduction in GAG accumulation in the CNS or in cartilage as measured by a reduction in vacuolation. Biochemically a reduction (62% in the cerebrum and 40% in the cerebellum) was demonstrated in IDU-PC-005 as compared to the untreated MPS I dogs.

The preclinical pharmacodynamic studies submitted in the IND suggest that enzyme replacement with rhIDU is effective in reducing the GAG accumulation in several soft tissues including the liver, spleen, lymph nodes, adrenal glands, small intestine, gall bladder and joint synovium in the both canine and feline MPS I disease models as determined by histology. However, the clinical significance of these histologic findings was not directly addressed in the studies and the lack of histologically significant changes in GAG accumulation in cartilage and the central nervous system suggest that the treatment may not prove effective against the orthopedic and cognitive manifestations of the clinical disease. The studies do not provide evidence that at the doses administered rhIDU is able to penetrate and accumulate to effective concentrations in cartilage and

central nervous system tissues, however the studies do not preclude the possibility that a higher dose or more frequent dosing regimen may produce enzyme concentrations sufficient to produce histologically significant changes in GAG accumulation in tissues that appear resistant to the short-term treatment. It should be noted that in addition to biochemical effects (increases in a-L-iduronidase activity levels in most tissues, decreases in GAG levels in tissues and urine, and histopathological evidence of tissue and organ improvement) demonstrated in the short term animal models long-term treatment of MPS I dogs (up to 74 weeks) with rhIDU resulted in improvement of clinical symptoms.

Subsequent formal toxicity studies in rats, dogs and monkeys further support the relative safety of rhIDU treatment. Of note there were only limited pharmacokinetic studies conducted and this topic should be addressed in more detail in post-marketing commitments. However the studies do suggest that the doses used in the clinical trial are sufficient to saturate a high affinity cellular receptor recognizing IDU. Acute toxicity studies were limited to a 15 day single dose IV study in the ----------rats and a single day repeat dose, dose escalation study in the ------. Neither study revealed toxicities. The primary toxicology study was a 26-week study in ---------- monkeys with 26 weekly IV bolus doses with a two-week recovery period. The highest dose used was 10 fold the dose used in the clinical trials. All monkeys in the high dose group had slightly elevated total leukocyte, lymphocytes, monocytes, and eosinophil counts that returned to normal levels after treatment (except eosinophils in males and monocytes in females). There was a single animal (152259) with a hypersensitivity reaction as described earlier in this section of the review. Approximately half of the monkeys developed anti-rhIDU antibodies. Neither the frequency nor the titer of the antibody was dose-related. The effect of the antibodies on pharmacokinetics was not well studied. Antibody production and pharmacokinetics can be further examined in phase IV studies. An eight-week repeat dose study was conducted to beagles to determine if changes in formulation effected the severity of infusion reactions. Although all the formulations tested exhibited infusion reactions after the third weekly dose the formulation incorporating Tween-80 produced the less severe reaction. Reproduction studies conducted in ----------rats failed to demonstrate deleterious effects on fertility, reproduction or development. In summary, the preclinical data adequately support use of the product, Aldurazyme^{TM}, for the indication specified by the sponsor.

M. David Green Ph.D., Branch Chief

Richard D. McFarland Ph.D., M.D., Medical Officer

Key Words; Hurler syndrome; Hurler-Scheie syndrome; Scheie Syndrome; Aldurazyme™; laronidase; mucopolysaccharidosis I; MPS I; α-L-iduronidase enzyme deficiency; lysosomes; lysosomal storage disease; antibodies; reproductive/developmental toxicity; non-human primate.

cc:
OTRR/DCTDA/CPT/MGreen

References

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